INFLUENCE OF AMORPHOUS SOLID DISPERSIONS OF PARACETAMOL AND PVP VA 64 ON THE THERMORESPONSIVE BEHAVIOUR OF THE POLYMER

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ABSTRACT

The dissolution of spray-dried amorphous solid dispersions consisting of paracetamol and PVP VA 64 at room temperature leads to the formation of different systems, depending on the drug/polymer ratio. Aqueous systems at room temperature with poor paracetamol/PVP VA 64 ratio are transparent solutions, while higher drug loads lead to phase separation of the solution. PVP VA 64 is known as thermoresponsive polymer. The aim of the study was to investigate the dissolution behaviour of these amorphous solid dispersions in water and their influence on the thermoresponsive behaviour of this polymer. Therefore, the demixing temperature was determined using DSC, since a change in the system constitutes an endothermic process. It could be shown that PVP VA 64 has lower critical solution temperature (LCST) behaviour around 70 °C, which decreases with increasing content of paracetamol due to the complex formation between the polymer and paracetamol.

Keywords: amorphous solid dispersion, thermoresponsive polymer, dissolution, lower critical solution temperature

INTRODUCTION

A large number of new active pharmaceutical ingredients shows poor water solubility. Amorphous solid dispersions (ASD) are a common approach to improve solubility and bioavailability. [Grohganz 2014]

The dissolution of ASD in water or physiological media can lead to super-saturation and two-phase separation, known as liquid liquid phase separation (LLPS) [Saboo, 2019].

Many polymers, which might be used for ASD, are known to separate into two phases when heating or cooling their aqueous solution. Two different behaviours of the so-called thermoresponsive polymers have to be distinguished: If the phase separation occurs during heating, the upper critical solution temperature (UCST) can be determined. If this happens during cooling, the lower critical solution temperature (LCST) can be measured. At this temperature, the system changes between one and two phases. A polymer-rich and polymer-poor phase are formed in the separated system. [Aseyev, 2011] Additives can increase or decrease the LCST [Van Durme, 2005].

The aim of the study was to investigate the dissolution behaviour of ASD, consisting of paracetamol and PVP VA 64, in water and their influence on the thermoresponsive behaviour of this polymer.

EXPERIMENTAL METHODS

Materials

Paracetamol was a generous gift from STADA, Germany. PVP VA 64 was kindly donated by BASF, Germany. Demineralized water was used for solutions.

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Amorphous solid dispersions (ASD)

Preparation of ASD was done by spray drying using a Büchi Mini-Spray Dryer B-191. Paracetamol and PVP VA 64 were dissolved in demineralized water in ratios of 1 : 9 (total concentration of mixture in aqueous solution 12.0 % (m/v)), 2 : 8 (6.0 %) and 3 : 7 (4.0 %). The following conditions were used for spray drying: inlet temperature 80 °C, outlet temperature 45 °C to 50 °C, pump rate 7 %, aspirator flow rate 100 %.

Physical mixture (PM)

The PM of drug and polymer (same ratios as for ASD) were mixed in a TURBULA® mixer for ten minutes.

Differential Scanning Calorimetry (DSC)

The solutions were analysed in aluminum pans on a Mettler Toledo DSC 1 with HSS7 sensor. The measurement was performed in duplicate at a heating rate of 5 K/min between -10 °C to 85 °C, depending on the estimated demixing temperature. The onset temperature of the endothermic process was determined [Van Durme, 2004]. All measurements were analysed under nitrogen purge.

RESULTS

Dissolution of ASD in water

Various systems made of paracetamol, PVP VA 64 and water (see Figure 1) were manufactured and optically evaluated at room temperature.

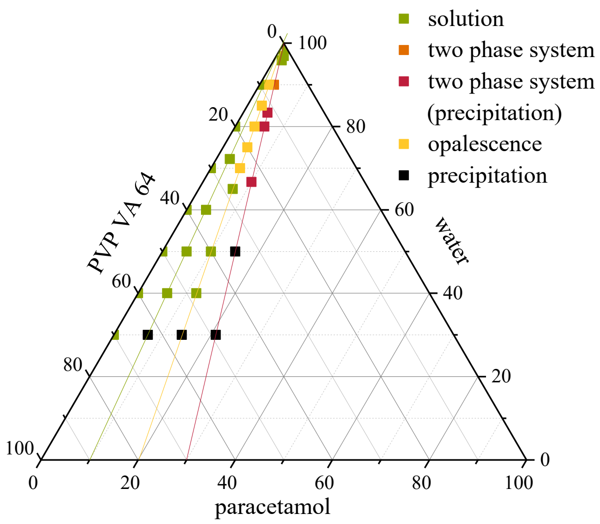

Figure 1: Ternary phase diagram of paracetamol, PVP VA 64 and water at room temperature.

Samples of the pure polymer and mixtures of paracetamol and the polymer in the ratio 1 : 9 (green line) show transparent solutions in water at room temperature, while mixtures in the ratio 2 : 8 (yellow line) are opalescent up to a concentration of 25 % PVP VA 64. Mixtures in the ratio 3 : 7 (red line) are in the form of an emulsion during stirring, while two-phase separation can be observed without moving the system.

LCST of ASD and PM

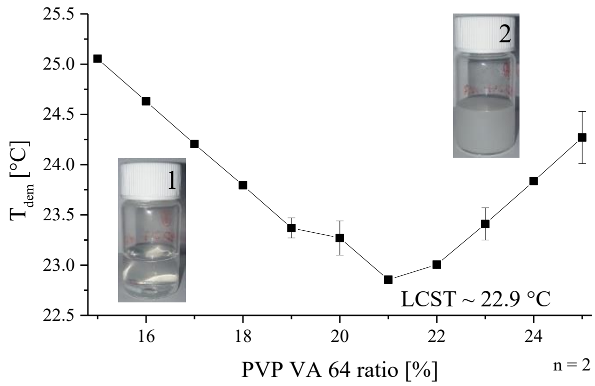

Figure 2: Demixing temperature (T_{dem}) of ASD 2 : 8 as a function of PVP VA 64 content; mean ± SD.

The demixing temperatures were determined for different concentrations of PVP VA 64. Below this temperatures the system is a transparent solution. In the near of the curve, the system becomes opalescent (see picture 1, Figure 2). Turbidity can be detected above the curve (see picture 2, Figure 2). Below the LCST there is a clear solution for each polymer concentration. The phase transition is reversible.

Table 1: LCST of ASD and PM for different systems.

Sample (PCM : PVP VA 64)	LCST ASD [°C]	LCST PM [°C]
pure PVP VA 64	-	69.7
1 : 9	52.6	53.4
2 : 8	22.4	22.9
3 : 7	14.2	14.7

The LCST decreases with increasing amount of paracetamol (absolute data not shown). The results for ASD and PM are similar for each ratio.

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DISCUSSION

A large number of polymers exhibits thermoresponsive behaviour in aqueous solution [Aseyev, 2011]. Below the LCST the polymer chains are hydrated and thus water-soluble, resulting in a transparent solution. Temperatures above LCST lead to aggregation of the polymer chains by hydrophobic interactions, which results in turbidity of the solution and later in phase separation. [Van Durme, 2005]

By forming a complex of paracetamol and PVP VA 64, the LCST decreases with increasing part of paracetamol. The formation of hydrogen bonds [Afrasiabi Garekani, 2003] or Van-der Waals forces [Wen, 2005] between the molecules are discussed as reasons.

The aqueous solutions of pure PVP VA 64 as well as ASD and PM in the ratio 1 : 9 are transparent at room temperature because their LCST is between 50 °C and 70 °C. Close to the critical point, solutions become opalescent [Monval, 1939]. The LCST of aqueous solutions of ASD and PM in the ratio 2 : 8 is around room temperature, resulting in opalescence.

Aqueous systems with drug/polymer ratio of 3 : 7 have a LCST that is lower than room temperature. Such mixtures result in an emulsion that separates rapidly into two phases when it is no longer shaken. The so-called liquid liquid phase separation is well known for ASD [Saboo, 2019]. Previous experiments have shown that on the one hand an aqueous, drug-poor phase with a drug concentration similar to the amorphous solubility results. On the other hand, a drug-rich phase is formed and it is discussed that it serves as a drug reservoir [Saboo, 2019].

CONCLUSIONS

It could be shown that PVP VA 64 is a thermoresponsive polymer with LCST behaviour. With increasing part of paracetamol the LCST decreases due to complex formation between the polymer and drug. The results for the different ratios are similar for ASD and PM.

As already mentioned, phase separated systems may act as drug reservoirs and therefore be of interest for modified drug release. The aim of the next investigation is to study the drug permeation from phase separated systems through Caco-2 cells.

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